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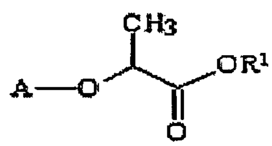
PROCESS FOR PREPARING (R)-ARYLOXYPROPIONIC ACID ESTER DERIVATIVES

Technical Field

The present invention relates to a method for preparing optically active (R)-aryloxypropionic acid ester derivatives, and more particularly to a method for preparing (R)-aryloxypropionic acid ester derivatives represented by the following formula 1 with high optical purity and good yields at low cost via nulceophilic substitution reaction using phenol derivatives with various substituted functional groups and (S)-alkyl O-arylsulfonyl lactates as reactants in the presence of a proper solvent and a base at optimum temperature :



(1)

wherein R^1 is a C_{1-6} -alkyl or benzyl group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a phenoxyphenol group, a pyridyloxyphenyl group and a phenyloxynaphthyl group, wherein the aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a C_{1-4} -alkyl group, a C_{1-4} -haloalkyl group, a C_{1-4} -alkoxy group, and a C_{1-4} -haloalkoxy group.

Background Art

The compound represented by Formula 1, commonly called (R)-propionic

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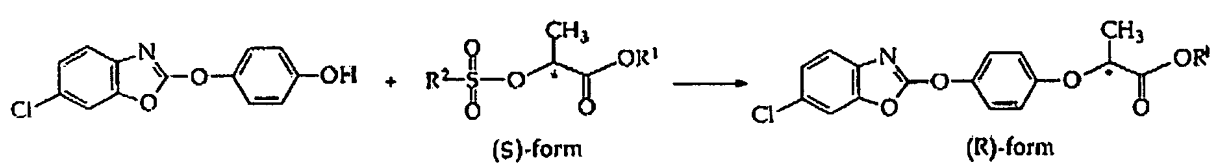
acid ester, is well known as a herbicidal substance that inhibits physiological functions of plants. Among them, a few compounds including (R)-ethyl 2-[4-(6-chloro-2-benzoxazolyloxy)phenoxy]propionate have been used as agrochemicals.

Due to the presence of a single chiral carbon, the 2-substituted propionic acid ester derivatives as represented above have optical isomers. In particular, it is known that their (R)-isomers have herbicidal activities while their (S)-isomers are of little herbicidal activities.

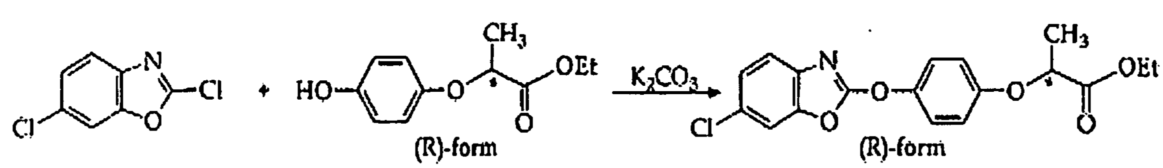
Preparation of propionic acid derivatives and their herbicidal activities have been disclosed in literatures [European Patent Nos. 157,225, 62,905, and 44,497; German Patent Nos. 3,409,201, 3,236,730, and 2,640,730].

The conventional methods of preparing propionic acid derivatives are well represented by the following two reaction schemes 1 and 2.

Scheme 1



Scheme 2



In the above methods of scheme 1, wherein substituted phenol and (S)-alkyl O-sulfonyl lactate are reacted, and scheme 2, wherein 2,6-dichlorobenzoxazole and (R)-ethyl 2-(4-hydroxyphenoxy)propionate are reacted, the reactions are performed in a polar solvent including acetonitrile to obtain (R)-fenoxaprop ethyl [yield = 70-

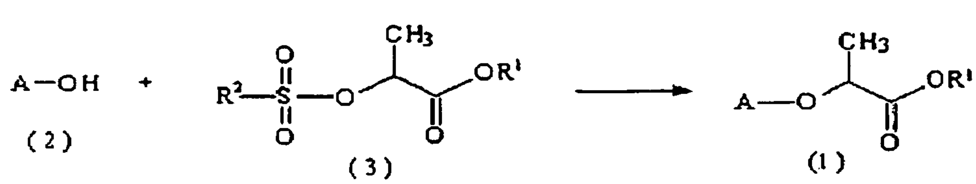
80%; optical purity = 60-90%].

However, these methods generate about 5-20% of (S)-isomers as by-products, which are not easily removed, and thus a rather complex process such as recrystallization is required to obtain pure (R)-fenoxaprop ethyl, thus increasing cost in preparation. Further, it is also a burden that starting materials, (R)-alkyl 2-(4-hydroxyphenoxy)propionates used in the reactions are to maintain high optical activity.

The inventors of the present invention focused on developing a novel method for preparing (R)-propionic acid ester derivatives, which have high optical purity with good yield. In doing so, the inventors of the present invention realized that it is important to find an appropriate condition for nucleophilic substitution reaction that prevents racemization of propionic acid ester derivatives. Accordingly, an object of the present invention is to provide a novel method for preparing optically active (R)- propionic acid ester derivatives at low cost by preventing racemization.

Disclosure of Invention

The present invention relates to a method for preparing (R)-propionic acid ester derivatives with high optical purity by reacting phenol derivatives represented by the following Formula 2 and (S)-alkyl O-arylsulfonyl lactate represented by the following Formula 3 in the presence of alkali metal carbonate base in an aliphatic or aromatic hydrocarbon solvent at 60 - 100℃:



wherein R^1 is a C_{1-6} -alkyl or benzyl group; R^2 is a C_{1-6} -alkyl, phenyl group, or a phenyl group substituted with a C_{1-6} -alkyl or a C_{1-6} -alkoxy group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, a quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a phenoxyphenol group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein said aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a C_{1-4} -alkyl group, a C_{1-4} -haloalkyl group, a C_{1-4} -alkoxy group, and a C_{1-4} -haloalkoxy group.

Hereinafter, the present invention is described in more detail.

The present invention relates to a method for preparation of optically active (R)-propionic acid ester derivatives with high yield and good optical purity via nucleophilic substitution reaction using phenol derivatives and (S)-alkyl O-arylsulfonyl lactates as reactants, wherein the reactions are performed under a condition of solvent, temperature and leaving group, which are all specifically designed.

Phenol derivatives and (S)-alkyl O-arylsulfonyl lactates, reactants of the present invention as represented by the above Formulas 2 and 3, are known compounds and are synthesized by the known methods. For example, (6-chloro-2-benzoxazolyloxy)phenol can be prepared by a 4-step reaction using commercially available substances, such as aminophenol, urea, sulfuryl chloride, phosphorus pentachloride, and triethylamine, and solvents, such as xylene, acetic acid, chlorobenzene, and dichloroethane. And, (S)-alkyl O-arylsulfonyl lactate can be prepared by reacting (S)-alkyl lactate and arylsulfonyl chloride in the presence of triethylamine in dichloroethane solvent.

In the nucleophilic substitution reaction of the present invention, selection of

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the reaction solvent plays a crucial role in preventing racemization. As a reaction solvent, aliphatic or aromatic hydrocarbon solvents such as xylene, toluene, benzene, cyclohexane, methylcycloheane, *n*-hexane, and *n*-heptane, etc. can be used, and cyclohexane and xylene are preferred among them.

The reaction temperature is also a very important factor to prevent racemization. A temperature range of 60 - 100℃ is appropriate, but considering reaction time and convenience, reflux temperature of cyclohexane (~80℃) is particularly preferable.

As a base of the present invention, alkali metal carbonates such as sodium carbonate, potassium carbonate, etc., can be used. Production of metal salt of phenol as an intermediate using the alkali metal carbonate as a base can greatly reduce unnecessary side reactions. Further, the above base is preferred to be powder (400-700 mesh) rather than pellets because powder form can reduce reaction time.

In the nucleophilic substitution reaction according to the present invention, water is generated as a byproduct while phenol-metal salt is produced as a main reaction intermediate. Thus generated water is removed by use of a specifically selected solvent in the present invention and this leads to a more effective prevention of racemization of products as well as hydrolysis of ester.

Upon completion of the nucleophilic substitution reaction, the sulfonic acid salt is filtered without cooling, and the filtrate is condensed to obtain (R)-propionic acid ester derivatives represented by Formula 1, the target compound of the present invention with high yields and good optical purity.

This invention is further illustrated by the following examples, however, these examples should not be construed as limiting the scope of this invention in any manner.

Best Mode for Carrying Out the Invention

Example 1

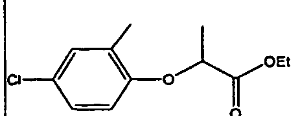
Preparation of (D+)-ethyl-2-(4-chloro-2-methylphenoxy)propionate (compound 1)

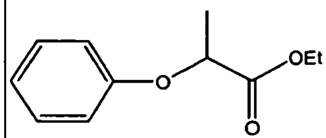
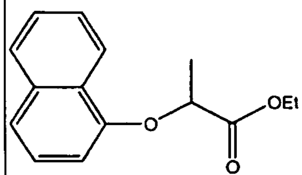
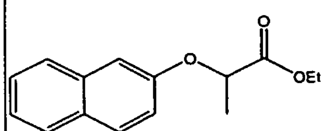
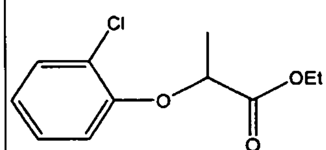
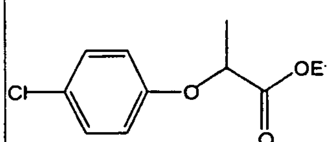
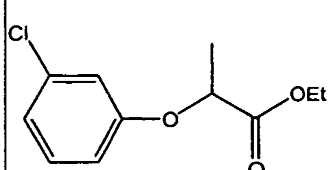
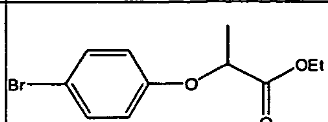
30mL of cyclohexane, 1.43g (10mmol) of 4-chloro-2-methylphenol, 2.86g (10.5mmol) of (S)-ethyl O-*p*-toluenesulfonyl lactate, and 2.76g (20mmol) of powdery K_2CO_3 were put in a 50mL flask equipped with a cooling condenser-attached Dean-Stock and reacted for 17 hours while refluxing. The reaction mixture was filtered without cooling and the solid cake was washed with 20mL of warm cyclohexane. The cyclohexane layer, the filtrate, was condensed to obtain 2.26g of the target compound (yield = 93%; purity = 98%; optical purity = 99.4%).

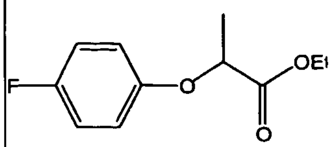
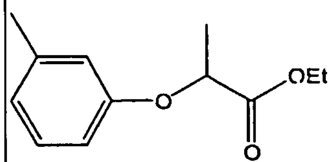
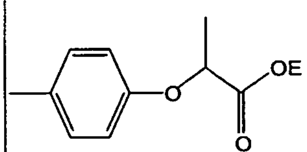
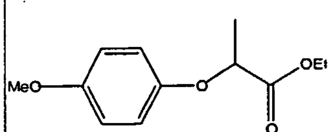
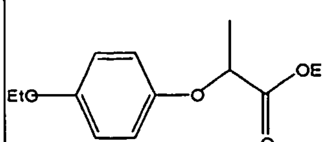
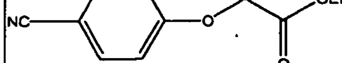
Rf=0.68(EA:Hx=1:4); 1H NMR(CDCl3, 200MHz) δ 1.24(t, *J*=7.2Hz, 3H), 1.62(d, *J*=6.8Hz, 3H), 2.25(s, 3H), 4.20(q, *J*=7.2Hz, 2H), 4.69(q, *J*=6.8Hz, 1H), 6.58 ~ 7.13(m, 3H); MS(70eV) m/z 244(M+), 242(M+), 169, 142, 125, 107, 89, 77

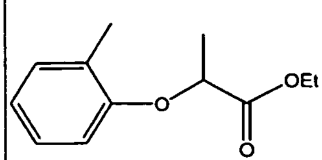
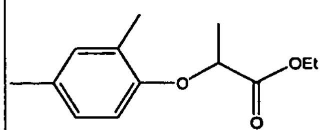
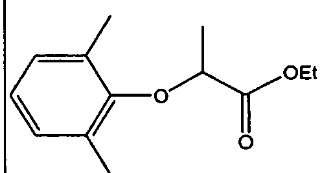
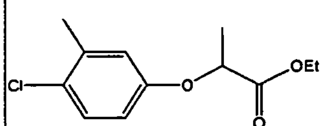
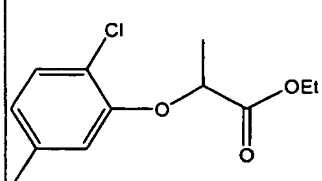
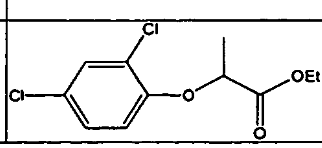
The following Table 1 shows the yield, ratio of generated optical isomers and spectral data of the compounds (1-25) performed the same as in Example 1.

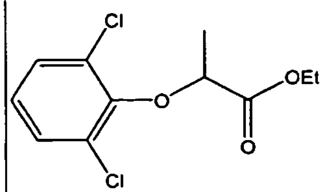
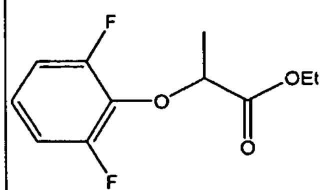
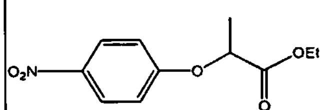
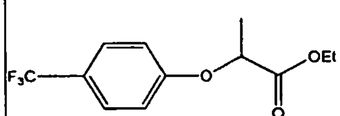
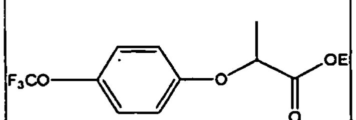
Table 1

comp. no.	structure	R/S ratio	yields	mp, R_f, NMR, MS
1		99.4 /0.6	93%	yellow liquid; R_f=0.68(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) δ1.24(t, *J*=7.2Hz, 3H), 1.62(d, *J*=6.8Hz, 3H), 2.25(s, 3H), 4.20(q, *J*=7.2Hz, 2H), 4.69(q, *J*=6.8Hz, 1H), 6.58 ~ 7.13(m, 3H); MS(70eV) m/z 244(M^+), 242(M^+), 169, 142, 125, 107, 89, 77

2		83.0/17.0	70%	white liquid; R_f=0.71(EA:Hx=1:3); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.24(t, *J*=7.1Hz, 3H), 1.62(d, *J*=6.8Hz, 3H), 4.21(q, *J*=7.2Hz, 2H), 4.74(q, *J*=6.8Hz, 1H), 6.93~7.27(m, 5H); MS(70eV) m/z 194(M$^+$), 121, 94, 77,58, 43
3		86.3/13.7	76%	yellow liquid; R_f=0.70(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.22(t, *J*=7.2Hz, 3H), 1.75(d, *J*=6.8Hz, 3H), 4.21(q, *J*=7.2Hz, 2H), 4.92(q, *J*=6.8Hz, 1H), 6.67~8.38(m, 7H); MS(70eV) m/z 244(M$^+$), 199, 171, 144, 127, 115, 101, 89
4		88.0/12.0	82%	yellow liquid; R_f=0.63(EA:Hx=1:4) ; ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.24(t, *J*=7.1Hz, 3H), 1.68(d, *J*=6.8Hz, 3H), 4.23(q, *J*=7.2Hz, 2H), 4.89(q, *J*=6.8Hz, 1H), 7.04~7.77(m, 7H); MS(70eV) m/z 244(M$^+$), 199, 171, 144, 127, 115, 101, 89
5		100.0/0.0	97%	yellow liquid; R_f=0.67(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.25(t, *J*=7.1Hz, 3H), 1.68(d, *J*=7.0Hz, 3H), 4.22(q, *J*=7.2Hz, 2H), 4.75(q, *J*=6.8Hz, 1H), 6.83~7.40(m, 4H); MS(70eV) m/z 230(M$^+$), 228(M$^+$), 193, 194, 155, 128, 111, 99, 91
6		84.9/15.1	98%	yellow liquid; R_f=0.70(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.25(t, *J*=7.1Hz, 3H), 1.61(d, *J*=7.0Hz, 3H), 4.21(q, *J*=7.1Hz, 2H), 4.70(q, *J*=6.8Hz, 1H), 6.78~7.25(m, 4H); MS(70eV) m/z 230(M$^+$), 228(M$^+$), 155, 128, 111, 99, 91, 75
7		97.2/2.8	96%	yellow liquid, R_f=0.65(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.26(t, *J*=7.1Hz, 3H), 1.62(d, *J*=7.0Hz, 3H), 4.23(q, *J*=7.2Hz, 2H), 4.72(q, *J*=6.9Hz, 1H), 6.73~7.23(m, 4H); MS(70eV) m/z 230(M$^+$), 228(M$^+$), 155, 128, 111, 99, 91, 75
8		96.7/3.3	96%	white liquid; R_f=0.60(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.25(t, *J*=7.1Hz, 3H), 1.61(d, *J*=7.0Hz, 3H), 4.21(q, *J*=7.2Hz, 2H), 4.68(q, *J*=6.8Hz,

				1H), 6.74~7.39(m, 4H); MS(70eV) m/z 272(M$^+$), 199, 172, 155, 120, 91
9		94.9 /5.1	95%	white liquid; R_f=0.72(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.25(t, *J*=7.1Hz, 3H), 1.60(d, *J*=7.0Hz, 3H), 4.21(q, *J*=7.0Hz, 2H), 4.67(q, *J*=6.8Hz, 1H), 6.79~7.00(m, 4H); MS(70eV) m/z 212(M$^+$), 139, 112, 95, 83
10		93.3 /6.7	98%	white liquid; R_f=0.68(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.25(t, *J*=7.1Hz, 3H), 1.60(d, *J*=7.0Hz, 3H), 2.31(s, 3H), 4.22(q, *J*=7.2Hz, 2H), 4.73(q, *J*=6.8Hz, 1H), 6.64~7.18(m, 4H); MS(70eV) m/z 208(M$^+$), 135, 108, 91, 77, 65
11		94.3 /5.7	94%	white liquid; R_f=0.68(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.25(t, *J*=7.2Hz, 3H), 1.60(d, *J*=6.8Hz, 3H), 2.27(s, 3H), 4.21(q, *J*=7.2Hz, 2H), 4.70(q, *J*=6.8Hz, 1H), 6.76~7.10(m, 4H); MS(70eV) m/z 208(M$^+$), 135, 107, 91, 77, 65
12		95.4 /4.6	88%	white liquid; R_f=0.42(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 300MHz) : δ 1.25(t, *J*=7.1Hz, 3H), 1.59(d, *J*=6.8Hz, 3H), 3.75(s, 3H), 4.21(q, *J*=7.1Hz, 2H), 4.65(q, *J*=6.8Hz, 1H), 6.78~6.86(m, 4H); MS(70eV) m/z 224(M$^+$), 151, 123, 109, 92, 77, 64
13		98.1 /2.9	82%	white liquid; R_f=0.51(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 300MHz) : δ 1.25(t, *J*=7.2Hz, 3H), 1.38(t, *J*=7.1Hz, 3H), 1.59(d, *J*=6.9Hz, 3H), 3.96(q, *J*=6.9Hz, 2H), 4.21(q, *J*=7.2Hz, 2H), 4.80(q, *J*=6.8Hz, 1H), 6.78~6.84(m, 4H); MS(70eV) m/z 238(M$^+$), 165, 137, 109, 91, 81, 65
14		100. 0/0. 0	100%	white liquid; R_f=0.48(EA:Hx=1:2); ^{1}H NMR($CDCl_3$, 300MHz) : δ 1.26(t, *J*=7.2Hz, 3H), 1.65(d, *J*=6.6Hz, 3H), 4.23(q, *J*=7.2Hz, 2H), 4.73(q, *J*=6.9Hz,

				1H), 6.90~7.60(m, 4H); MS(70eV) m/z 219(M^+), 146, 119, 102, 91, 73, 65
15		94.6 /5.4	96%	white liquid; R_f=0.69(EA:Hx=1:4); ^1H NMR($CDCl_3$, 200MHz) : δ 1.24(t, J=7.2Hz, 3H), 1.62(d, J=6.6Hz, 3H), 2.28(s, 3H), 4.21(q, J=7.2Hz, 2H), 4.73(q, J=6.8Hz, 1H), 6.66~7.16(m, 4H); MS(70eV) m/z 208(M^+), 135, 108, 91, 77, 65, 55
16		94.6 /5.4	87%	white liquid; R_f=0.76(EA:Hx=1:4); ^1H NMR($CDCl_3$, 200MHz) : δ 1.25(t, J=7.2Hz, 3H), 1.61(d, J=6.8Hz, 3H), 2.24(s, 6H), 4.20(q, J=7.2Hz, 2H), 4.68(q, J=6.8Hz, 1H), 6.57~6.95(m, 3H); MS(70eV) m/z 222(M^+), 149, 122, 105, 91, 77
17		98.0 /2.0	75%	yellow liquid; R_f=0.74(EA:Hx=1:4); ^1H NMR($CDCl_3$, 200MHz) : δ 1.28(t, J=7.2Hz, 3H), 1.53(d, J=6.6Hz, 3H), 2.29(s, 6H), 4.25(q, J=7.2Hz, 2H), 4.49(q, J=6.8Hz, 1H), 6.90~7.02(m, 3H); MS(70eV) m/z 222(M^+), 149, 122, 105, 91, 77, 65, 53
18		94.4 /5.6	96%	white liquid; R_f=0.72(EA:Hx=1:4); ^1H NMR($CDCl_3$, 200MHz) : δ 1.25(t, J=7.2Hz, 3H), 1.60(d, J=6.8Hz, 3H), 2.32(s, 3H), 4.22(q, J=7.2Hz, 2H), 4.69(q, J=6.8Hz, 1H), 6.61~7.23(m, 3H); MS(70eV) m/z 244(M^+), 242(M+), 169, 125, 142, 107, 99, 89
19		94.9 /5.1	95%	white liquid; R_f=0.65(EA:Hx=1:4); ^1H NMR($CDCl_3$, 200MHz) : δ 1.25(t, J=7.2Hz, 3H), 1.60(d, J=6.8Hz, 3H), 2.32(s, 3H), 4.22(q, J=7.2Hz, 2H), 4.69(q, J=6.8Hz, 1H), 6.60~7.23(m, 3H); MS(70eV) m/z 244(M^+), 242(M+), 169, 142, 125, 107, 99, 89
20		100. 0/0. 0	91%	white liquid; R_f=0.63(EA:Hx=1:4); ^1H NMR($CDCl_3$, 200MHz) : δ 1.25(t, J=7.2Hz, 3H), 1.67(d, J=6.8Hz, 3H),

				4.22(q, J=7.0Hz, 2H), 4.71(q, J=6.8Hz, 1H), 6.76~7.39(m, 3H); MS(70eV) m/z 263(M$^+$), 262(M+), 189, 162, 154, 145, 133, 125, 109, 101, 73
21		100.0/0.0	92%	white liquid; R_f=0.60(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.28(t, J=7.2Hz, 3H), 1.63(d, J=6.6Hz, 3H), 4.25(q, J=7.2Hz, 2H), 4.83(q, J=7.0Hz, 1H), 6.95~7.33(m, 3H); MS(70eV) m/z 263(M$^+$), 262(M+), 227, 189, 162, 145, 133, 125, 109, 101, 73
22		100.0/0.0	94%	white liquid; R_f=0.68(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.27(t, J=7.2Hz, 3H), 1.63(d, J=6.8Hz, 3H), 4.22(q, J=7.0Hz, 2H), 4.81(q, J=7.0Hz, 1H), 6.84~7.00(m, 3H); MS(70eV) m/z 230(M$^+$), 157, 130, 113, 101, 82, 73
23		100.0/0.0	67%	yellow liquid; R_f=0.50(EA:Hx=1:2); ^{1}H NMR($CDCl_3$, 300MHz) : δ 1.26(t, J=7.2Hz, 3H), 1.68(d, J=6.6Hz, 3H), 4.24(q, J=7.1Hz, 2H), 4.85(q, J=7.2Hz, 1H), 6.90~8.22(m, 4H); MS(70eV) m/z 239(M$^+$), 166, 120, 91, 76
24		97.9/2.1	79%	white liquid; R_f=0.70(EA:Hx=1:2); ^{1}H NMR($CDCl_3$, 300MHz) : δ 1.25(t, J=7.1Hz, 3H), 1.64(d, J=6.8Hz, 3H), 4.23(q, J=7.1Hz, 2H), 4.79(q, J=6.8Hz, 1H), 6.92~7.55(m, 4H); MS(70eV) m/z 262(M$^+$), 243, 189, 162, 145
25		96.8/3.2	86%	white liquid; R_f=0.72(EA:Hx=1:2); ^{1}H NMR($CDCl_3$, 300MHz) : δ 1.25(t, J=7.2Hz, 3H), 1.62(d, J=6.6Hz, 3H), 4.22(q, J=7.2Hz, 2H), 4.71(q, J=6.8Hz, 1H), 6.85~7.14(m, 4H); MS(70eV) m/z 278(M$^+$), 205, 178, 109, 91

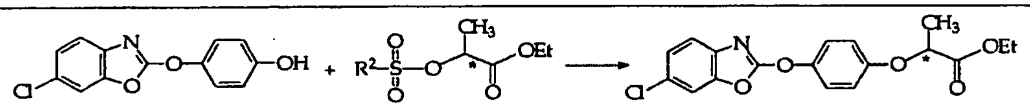
Example 2

Preparation of (D+)-ethyl-2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propionate (Compound 26, Commercial Name: Fenoxaprop-p-ethyl)

50mL of cyclohexane, 2.61g (10mmol) of (6-chloro-2-benzoxazolyloxy)phenol, 2.86g (10.5mmol) of (S)-ethyl O-*p*-toluenesulfonyl lactate, and 2.76g (20mmol) of powdery K_2CO_3 were put in a 100mL flask equipped with a cooling condenser-attached Dean-Stock and reacted for 12 hours while refluxing. The reaction mixture was filtered without cooling and the solid cake was washed with 20mL of warm cyclohexane. The cyclohexane layer, the filtrate, was condensed to obtain 3.20g of the target compound (yield = 89%; purity = 98%; optical purity = 99.9%). mp 82 ~ 84 ℃(observed); Rf=0.52(hexane/ethylacetate=3/1); 1H-NMR(CDCl3, 200MHz) δ 1.13(t, *J*=7.1Hz, 3H), 1.81(d, *J*=6.9Hz, 3H), 4.22(q, *J*=7.1Hz, 2H), 4.72(q, *J*=6.9Hz, 1H), 6.99 ~ 7.42(m, 7H); MS(70 eV) m/z 363(M+), 361(M+), 291, 288, 263, 261, 182, 144, 119, 91.

The following Table 2 shows yields and ratio of optical isomers generated in the course of substitution reactions performed the same as in Example 2.

Table 2



Reaction Solvent	R^2	Reaction Temperature	Reaction Time	Yields (g, %)	Ratio of (R)/(S) Isomers*(%)
Cyclohexane	*p*-toluyl	Reflux	12 hours	3.20g, 89%	99.9/0.1
Methylcyclohexane	*p*-toluyl	Reflux	12 hours	3.20g, 89%	98.5/1.5
n-Hexane	*p*-toluyl	Reflux	24 hours	2.80g, 77.5%	99.9/0.1
Xylene	*p*-toluyl	100℃	12 hours	3.10g, 85.5%	99.9/0.1

Cyclohexane	Phenyl	Reflux	12 hours	3.20g, 89%	99.9/0.1
Cyclohexane	Methyl	Reflux	12 hours	3.20g, 89%	95.0/5.0
*Ratio of (R)/(S) isomers: Identified by LC					

Example 3

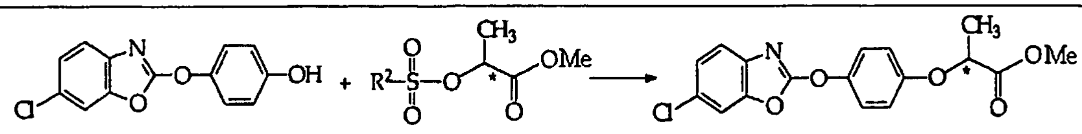
Preparation of (D+)-methyl- 2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propionate (Compound 27)

50mL of cyclohexane, 2.61g (10mmol) of (6-chloro-2-benzoxazolyloxy)phenol, 2.35g (10.5mmol) of (S)-methyl O-(*p*-methoxybenzene)sulfonyl lactate, and 2.12g (20mmol) of powdery Na_2CO_3 were put in a 100mL flask equipped with a cooling condenser-attached Dean-Stock and reacted for 12 hours while refluxing. The reaction mixture was filtered without cooling and the solid cake was washed with 20mL of warm cyclohexane. The cyclohexane layer, the filtrate, was condensed to obtain 3.10g of the target compound (yield = 89%; purity = 98%; optical purity = 99.9%).

mp 97 ℃(observed); Rf=0.50(hexane/ethylacetate=3/1); 1H-NMR(CDCl3, 200MHz) δ 1.51(d, *J*=6.4Hz, 3H), 3.70(s,3H), 4.55(q, *J*=6.4Hz, 1H), 6.84 ~ 7.40(m, 7H); MS(70 eV) m/z 349(M+), 347(M+), 291, 288, 263, 261, 182, 144, 119, 91.

The following Table 3 shows yields and ratio of optical isomers generated in the course of substitution reactions performed the same as in Example 3.

Table 3



Reaction Solvent	R^2	Reaction Temperatu -re	Reactio n Time	Yields (g, %)	Ratio of (R)/(S) Isomers*(%)

Cyclohexane	*p*-Methoxyphenyl	Reflux	12 hours	3.10g, 89%	99.9/0.1
Methylcyclohexane	*p*-Methoxyphenyl	Reflux	12 hours	3.10g, 89%	98.5/1.5
n-Heptane	*p*-Methoxyphenyl	Reflux	20 hours	2.70g, 77.7%	99.9/0.1
Xylene	*p*-Methoxyphenyl	100℃	10 hours	3.10g, 89%	99.9/0.1
Cyclohexane	Methyl	Reflux	12 hours	3.05g, 87.7%	95.0/5.0
Cyclohexane	Phenyl	Reflux	12 hours	3.05g, 87.7%	99.9/0.1
*Ratio of (R)/(S) isomers: Identified by LC					

Example 4

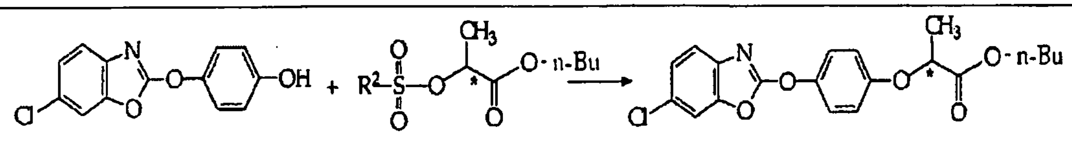
Preparation of (D+)-*n*-butyl- 2-[4-(6-chloro-2-benzoxazolyloxy)-phenoxy]-propionate (Compound 28)

50mL of cyclohexane, 2.61g (10mmol) of (6-chloro-2-benzoxazolyloxy)phenol, 3.15g (10.5mmol) of (S)-*n*-butyl O-*p*-toluenesulfonyl lactate, and 2.76g (20mmol) of powdery K_2CO_3 were put in a 100mL flask equipped with a cooling condenser-attached Dean-Stock and reacted for 12 hours while refluxing. The reaction mixture was filtered without cooling and the solid cake was washed with 20mL of warm cyclohexane. The cyclohexane layer, the filtrate, was condensed to obtain 3.60g of the target compound (yield = 92.3%; purity = 98%; optical purity = 99.9%).

mp 48 ~ 50℃(observed); Rf=0.59(hexane/ethylacetate=3/1); 1H-NMR(CDCl3, 200MHz) δ 0.91(t, J=7.1Hz, 3H), 1.48 ~ 1.58(m, 4H), 1.51(d, J=6.9Hz, 3H), 4.26(q, J=7.1Hz, 2H), 4.45(q, J=6.9Hz, 1H), 6.84 ~ 7.40(m, 7H); MS(70 eV) m/z 391(M+), 389(M+), 291, 288, 263, 261, 182, 144, 119, 91.

The following Table 4 shows yields and ratio of optical isomers generated in the course of substitution reactions performed in Example 4.

Table 4



Reaction Solvent	R^2	Reaction Temperatu-re	Reaction Time	Yields (g, %)	Ratio of (R)/(S) Isomers (%)*
Cyclohexane	*p*-Toluyl	Reflux	12 hours	3.60g, 92.3%	99.9/0.1
Methylcyclohexane	*p*-Toluyl	Reflux	12 hours	3.60g, 92.3%	98.5/1.5
n-Heptane	*p*-Toluyl	Reflux	10 hours	3.30g, 84.7%	99.9/0.1
Xylene	*p*-Toluyl	100℃	10 hours	3.50g, 89.8%	99.9/0.1
Xylene	*p*-Toluyl	110℃	10 hours	3.50g, 89.8%	95.0/5.0
Cyclohexane	Methyl	Reflux	12 hours	3.50g, 89.8%	95.0/5.0
Cyclohexane	Phenyl	Reflux	12 hours	3.50g, 89.8%	99.9/0.1

*Ratio of (R)/(S) isomers: Identified by LC

Example 5

Preparation of (D+)-*n*-ethyl-2-[4-(3-chloro-5-trifluoromethylpyridine-yloxy)-phenoxy]-propionate (Compound 29)

30mL of cyclohexane, 2.90g (10mmol) of 4-(3-chloro-5-trifluoromethylpyridinyloxy)phenol, 2.86g (10.5mmol) of (S)-ethyl O-*p*-toluenesulfonyl lactate, and 2.76g (20mmol) of powdery K_2CO_3 were put in a 50mL flask equipped with a cooling condenser-attached Dean-Stock and reacted for 18 hours while refluxing. The reaction mixture was filtered without cooling and the solid cake was washed with 20mL of warm cyclohexane.The cyclohexane layer, the filtrate, was condensed to obtain 3.51g of the target compound (yield = 90%; purity = 98%; optical purity = 97.0%).

Rf=0.56(EA:Hx=1:4); 1H NMR(CDCl3, 200MHz) δ 1.27(t, *J*=7.2Hz, 3H), 1.63(d, *J*=6.6Hz, 3H), 4.24(q, *J*=7.2Hz, 2H), 4.73(q, *J*=6.90Hz, 1H), 6.89 ~ 8.27(m, 6H); MS(70eV) m/z 389(M+), 370, 316, 288, 272, 261, 226, 209, 180, 160, 119, 109, 91, 76, 63.

Example 6

Preparation of (D+)-*n*-ethyl-2-[4-(2,4-dichlorophenoxy)-phenoxy]-propionate (Compound 30)

30mL of cyclohexane, 2.55g (10mmol) of 4-(2,4-dichlorophenoxy)phenol, 2.86g (10.5mmol) of (S)-ethyl O-*p*-toluenesulfonyl lactate, and 2.76g (20mmol) of powdery K_2CO_3 were put in a 50mL flask equipped with a cooling condenser-attached Dean-Stock and reacted for 17 hours while refluxing. The reaction mixture was filtered without cooling and the solid cake was washed with 20mL of warm cyclohexane. The cyclohexane layer, the filtrate, was condensed to obtain 2.74g of the target compound (yield = 77%; purity = 98%; optical purity = 94.6%).

Rf=0.77(EA:Hx=1:2); 1H NMR(CDCl3, 300MHz) δ 1.26(t, *J*=7.2Hz, 3H), 1.62(d,

J=6.9Hz, 3H), 4.23(q, *J*=7.1Hz, 2H), 4.69(q, *J*=6.7Hz, 1H), 6.78 ~ 7.44(m, 7H); MS(70eV) m/z 355(M+), 354(M+), 281, 253, 202, 184, 173, 162, 139, 120, 109, 91.

Example 7

Preparation of (D+)-*n*-ethyl-2-[7-(2-chloro-4-trifluoromethylphenoxy)-naphthalene-2-yloxy]propionate (Compound 31))

30mL of cyclohexane, 3.39g (10mmol of 7-(2-chloro-4-trifluoromethylphenoxy)-2-naphthalenol, 2.86g (10.5mmol) of (S)-ethyl O-*p*-toluenesulfonyl lactate, and 2.76g (20mmol) of powdery K_2CO_3 were put in a 50mL flask equipped with a cooling condenser-attached Dean-Stock and reacted for 19 hours while refluxing. The reaction mixture was filtered without cooling and the solid cake was washed with 20mL of warm cyclohexane.The cyclohexane layer, the filtrate, was condensed to obtain 4.08g of the target compound (yield = 93%; purity = 98%; optical purity = 92.8%).

Rf=0.60(EA:Hx=1:4); 1H NMR(CDCl3, 300MHz) δ 1.24(t, *J*=7.2Hz, 3H), 1.67(d, *J*=6.9Hz, 3H), 4.23(q, *J*=5.7Hz, 2H), 4.86(q, *J*=6.9Hz, 1H), 6.94 ~ 7.81(m, 9H); MS(70eV) m/z 438(M+), 365, 338, 321, 303, 286, 275, 170, 142, 126, 114, 102.

Example 8

Preparation of (D+)-*n*-ethyl-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate (Compound 32)

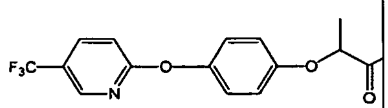
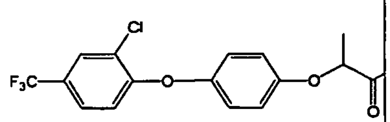
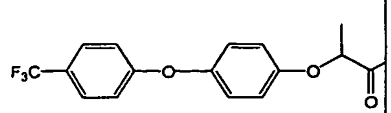
30mL of cyclohexane, 2.73g (10mmol) of 4-(6-chloroquinoxalin-2-yloxy)phenol, 2.86g (10.5mmol) of (S)-ethyl O-*p*-toluenesulfonyl lactate, and 2.76g (20mmol) of powdery K_2CO_3 were put in a 50mL flask equipped with a cooling condenser-attached Dean-Stock and reacted for 18 hours while refluxing. The reaction mixture was filtered without cooling and the solid cake was washed with

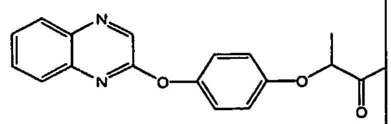
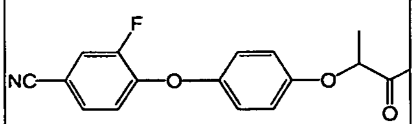
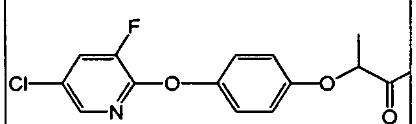
20mL of warm cyclohexane. The cyclohexane layer, the filtrate, was condensed to obtain 3.39g of the target compound (yield = 91%; purity = 98%; optical purity = 99.8%).

mp=60 ~ 61℃(R observed), mp=83 ~ 84℃(R,S observed), Rf=0.63(EA:Hx=1:2); 1H NMR(CDCl3, 500MHz) δ 1.29(t, J=7.1Hz, 3H), 1.65(d, J=6.8Hz, 3H), 4.26(m, 2H), 4.76(q, J=6.8Hz, 1H), 6.95 ~ 8.67(m, 7H); MS(70eV) m/z 372(M+), 299, 272, 255, 244, 212, 199, 163, 155, 136, 110, 100, 91, 65.

The following Table 1 shows the yield, ratio of generated optical isomers and spectral data of the compounds (33-38) performed in Example 8.

Table 5

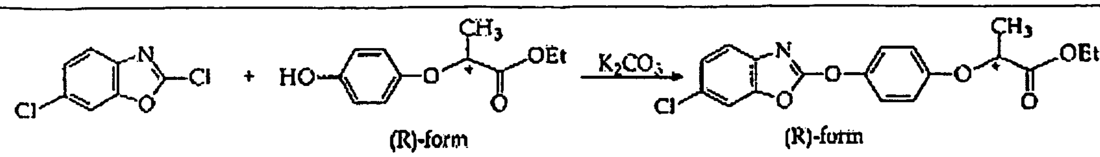
comp. no.	structure	R/S ratio	yields	mp, R_f, NMR, MS
33		99.3/ 0.7	92%	white solid, mp=33~35℃; R_f=0.58(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.28(t, J=7.2Hz, 3H), 1.63(d, J=6.8Hz, 3H), 4.24(q, J=7.1Hz, 2H), 4.73(q, J=6.8Hz, 1H), 6.94~8.44(m, 7H); MS(70eV) m/z 355(M^+), 336, 282, 254, 227, 198, 146, 126, 91, 76
34		96.9/ 3.1	94%	yellow liquid; R_f=0.75(EA:Hx=1:2); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.27(t, J=7.2Hz, 3H), 1.63(d, J=6.4Hz, 3H), 4.24(q, J=7.1Hz, 2H), 4.72(q, J=6.8Hz, 1H), 6.83~7.71(m, 7H); MS(70eV) m/z 388(M^+), 369, 315, 288, 253, 236, 196, 179, 157, 120, 109, 91, 64
35		97.0/ 3.0	96%	white solid, mp=58~60℃; R_f=0.64(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.27(t, J=7.2Hz, 3H), 1.63(d, J=6.6Hz, 3H), 4.24(q, J=7.1Hz, 2H), 4.72(q, J=6.8Hz, 1H),

				6.87~7.56(m, 8H); MS(70eV) m/z 354(M+), 335, 281, 254, 209, 177, 168, 145, 120, 109
36		96.0/ 4.0	85%	white solid, mp=62~65℃; R_f=0.33(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.28(t, *J*=7.2Hz, 3H), 1.65(d, *J*=6.8Hz, 3H), 4.25(q, *J*=7.1Hz, 2H), 4.77(q, *J*=6.8Hz, 1H), 6.91~8.07(m, 9H); MS(70eV) m/z 338(M+), 310, 265, 237, 221, 155, 129, 102, 91, 75
37		99.9/ 0.1	90%	white liquid; R_f=0.54(EA:Hx=1:2); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.27(t, *J*=7.2Hz, 3H), 1.64(d, *J*=6.8Hz, 3H), 4.24(q, *J*=7.2Hz, 2H), 4.72(q, *J*=6.8Hz, 1H), 6.80~7.51(m, 7H); MS(70eV) m/z 329(M+), 310, 272, 256, 237, 229, 199, 184, 155, 120, 101, 91
38		99.1/ 09	92%	white solid, mp=48~50℃; R_f=0.58(EA:Hx=1:4); ^{1}H NMR($CDCl_3$, 200MHz) : δ 1.28(t, *J*=7.2Hz, 3H), 1.63(d, *J*=6.8Hz, 3H), 4.24(q, *J*=7.1Hz, 2H), 4.73(q, *J*=6.8Hz, 1H), 6.94~8.44(m, 7H); MS(70eV) m/z 340(M+), 267, 239, 212, 183, 131, 111, 91

Comparative Example 1

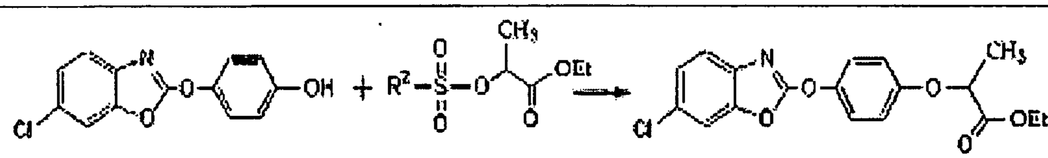
The following Tables 6 and 7 show yields and ratio of optical isomers generated in the course of preparing (D+)-methyl-2-[4-(6-chloro-2-benzoxazolyloxy)phenoxy]propionate (compound 27) according to the known methods shown in the reaction schemes 1 and 2.

Table 6



Reaction Solvent	Reaction Temperature	Reaction Time	Yields (%)	Ratio of (R)/(S) Isomers (%)*
Acetonitrile	Reflux	5 hours	80%	85.0/15.0
Methyl ethyl ketone	Reflux	5 hours	75%	80.0/20.0
Acetone	Reflux	15 hours	79%	80.0/20.0
Dimethylformamid-e	Reflux	4 hours	84%	75.0/25.0
Dichloromethane	Reflux	15 hours	64%	90.0/10.0
*Ratio of (R)/(S) isomers: Identified by LC				

Table 7



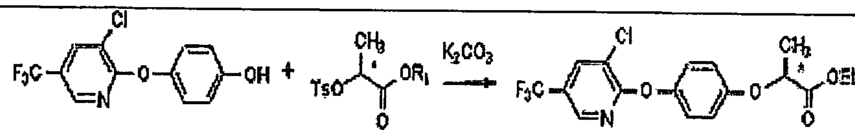
Reaction Solvent	R^2	Reaction Temperatu-re	Reactio n Time	Yields (%)	Ratio of (R)/(S) Isomers(%)*
Acetonitrile	*p*-Toluyl	Reflux	5 hours	85%	95.0/5.0
Methyl ethyl ketone	*p*-Toluyl	Reflux	5 hours	82%	95.0/5.0
Acetonitrile	Methyl	Reflux	5 hours	87%	85.0/15.0
Methyl ethyl	Methyl	Reflux	5 hours	85%	85.0/15.0

ketone					
*Ratio of (R)/(S) isomers: Identified by LC					

Comparative Example 2

The following Table 8 shows yields and ratio of optical isomers generated in the course of preparing (D+)-*n*-ethyl-2-[4-(3-chloro-5-trifluoromthylpyridine-2-yloxy)phenoxy]propionate (compound 29) according to the known methods shown in the reaction scheme 2.

Table 8



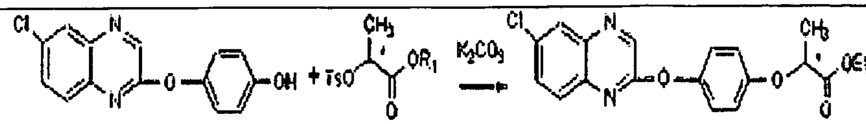
Reaction Solvent	Reaction Temperature	Reaction Time	Yield (%)	Ratio of (R)/(S) Isomers (%)*
Acetonitrile	Reflux	5 hours	72%	95.0/5.0
Methyl ethyl ketone	Reflux	5 hours	79%	80/20.0
Dimethylformamide	80 ~ 90℃	4 hours	70%	93.0/7.0
*Ratio of (R)/(S) isomers: Identified by LC				

Comparative Example 3

The following Table 9 shows yields and ratio of optical isomers generated in the course of preparing (D+)-*n*-ethyl-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate (compound 32) according to the known methods shown in the reaction scheme 2.

AMD 34 AMDT

Table 9



Reaction Solvent	Reaction Temperature	Reaction Time	Yields (%)	Ratio of (R)/(S) Isomers (%)*
Acetonitrile	Reflux	5 hours	66%	95.0/5.0
Methyl ethyl ketone	Reflux	5 hours	59%	95.0/5.0
Dimethylformamide	80 ~ 90℃	4 hours	63%	93.0/7.0
*Ratio of (R)/(S) isomers: Identified by LC				

Industrial Applicability

As described above, the preparing method of the present invention enables production of optically pure (R)-aryloxy propionic acid ester derivatives with good yield and is thus expected to produce an enormous economic effect.

While the present invention has been described in detail with reference to the preferred embodiments, those skilled in the art will appreciate that various modifications and substitutions can be made thereto without departing from the spirit and scope of the present invention as set forth in the appended claims.